X-Ray Crystal and Molecular Structure of *cis*(*NN'*),*trans*(*OO'*)-Bis-(2-aminoethanolato)-*cis*-dichloroplatinum(IV) Dihydrate. The Relationship of Anti-tumour Activity to Ring Closure †

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The title complex has been characterised by ^1H and ^{195}Pt n.m.r. spectroscopy and *X*-ray crystallography. The arrangement around the Pt^{IV} atom is closely octahedral with bidentate 2-aminoethanolate rather than unidentate 2-aminoethanol ligands. This finding is discussed in relation to its unusually low anti-tumour activity.

Square-planar Pt^{II} complexes containing two *cis* primary or secondary amines and two additional, more weakly bound, *cis* 'leaving groups' such as chloride ions invariably exhibit anti-tumour activity.[1] Many such complexes, however, exhibit poor solubility in water. This can be improved by a suitable choice of amine and also by incorporating an additional pair of *trans* dihydroxo-ligands, forming the analogous Pt^{IV} complex.[2] Cysteine is capable of reducing such Pt^{IV} complexes [3] and it seems likely that these Pt^{IV} complexes owe their activity to *in vivo* reduction. Little research had been reported until recently on the structures and reactivity of Pt^{IV} *trans*-dihydroxo-complexes. Curiously, we found that the hydroxo and chloride ligands of *trans,trans,trans*-$[Pt(NH_3)_2Cl_2(OH)_2]$ isomerised on recrystallisation of the complex from water.[4]

We report here studies of another Pt^{IV} diamine complex prepared by hydrogen peroxide oxidation of *cis*-$[Pt(NH_2CH_2CH_2OH)_2Cl_2]$ and initially thought to be *cis,cis,trans*-$[Pt(NH_2CH_2CH_2OH)_2Cl_2(OH)_2]$. However, we noted that the reported activity against L1210 leukaemia [5] was very low, giving a maximum $\%T/C$‡ value of 107, compared to 207 for *cis,cis,trans*-$[Pt(NH_2Pr^i)_2Cl_2(OH)_2]$. On the other hand, the Pt^{II} complex *cis*-$[Pt(NH_2CH_2CH_2OH)_2Cl_2]$ exhibits activity comparable to *cis*-$[Pt(NH_3)_2Cl_2]$ ($\%T/C$ *ca.* 158). Our n.m.r. and *X*-ray crystallographic studies show that the Pt^{IV} complex contains chelated, deprotonated 2-aminoethanol. This may be responsible for its low anti-cancer activity.

Experimental

A sample prepared by H_2O_2 oxidation of *cis*-$[Pt(NH_2CH_2CH_2OH)_2Cl_2]$ and thought to be *cis,cis,trans*-$[Pt(NH_2CH_2CH_2OH)_2Cl_2(OH)_2]$ was kindly supplied by the Johnson Matthey Research Centre, Sonning Common. It was recrystallised from water. The ^1H n.m.r. spectrum in D_2O was identical before and after recrystallisation except for the disappearance of a few small peaks near 3.76 p.p.m. The four multiplets at δ *ca.* 3.59, 3.09, 2.79, and 2.67 p.p.m. are shown in Figure 1. Hydrogen-1 n.m.r. spectra (400 MHz) were recorded in D_2O on the Bruker WH 400 spectrometer of University of London Intercollegiate Research Service. Platinum-195 n.m.r. measurements were made on a Bruker WM 200 spectrometer at 43.00 MHz and were referenced to $[PtCl_6]^{2-}$ at the same temperature as the sample.

† *Supplementary data available* (No. SUP 23524, 11 pp.): observed and calculated structure factors, thermal parameters. See Notices to Authors No. 7, *J. Chem. Soc., Dalton Trans.*, 1981, Index issue.

‡ $\%T/C$ is the ratio of median survival times in drug-treated (T) and untreated tumour control (C) groups of mice. Compounds with $\%T/C > 125$ are usually considered to be active.

X-Ray Crystallography.—Accurate cell dimensions were obtained by measurement of 25 θ values on an Enraf-Nonius CAD-4 diffractometer, following a preliminary examination of Weissenberg photographs. The intensity data were collected with Mo-K_α radiation, using the θ—2θ scan mode up to $\theta = 28°$. A periodic check on intensities of three strong reflections showed that crystal decay was occurring and so the intensity data were corrected for this anisotropically using the program CHORTA of the SDP program system. The maximum and average correction factors were 1.25 and 1.11, respectively. An empirical absorption correction was also made. The crystal system is triclinic, hence the possible space groups are $P1$ and $P\bar{1}$. The former was adopted initially, and subsequently replaced by the latter, as the structure showed an inversion centre between the two independent molecules in the space group of $P1$.

Crystal data. $C_4H_{16}Cl_2N_2O_4Pt$, $M = 442.18$, Triclinic, $a = 7.097(2)$, $b = 9.060(1)$, $c = 10.306(2)$ Å, $\alpha = 116.02(1)$, $\beta = 101.63(2)$, $\gamma = 69.21(1)°$, $U = 555.9(4)$ Å^3, $D_c = 2.522$ g cm^{-3}, $Z = 2$, $F(000) = 396$, space group $P\bar{1}$, μ(Mo-K_α) = 137.4 cm^{-1}, λ(Mo-K_α) = 0.7107 Å.

The structure was solved by the heavy-atom method. Out of 2 311 unique observed reflections, 2 051 with $I > 2.5\sigma(I)$ were used for the refinement. Both hydrogen atoms bonded to N(2), C(3), and O(W2), and one of the hydrogen atoms bonded to N(1), C(2), and O(W1) appeared clearly in the difference-Fourier map. However, some of them did not refine well, and had to be fixed at the positions found in this map. The rest of the hydrogen atoms were not revealed in the difference-Fourier map, therefore these were generated by assuming a near-ideal geometry, except for the other hydrogen atom bonded to O(W1), which could not be located. The final unweighted and weighted R factors were 0.030 and 0.036, respectively, with the weighting system $w = 1/[\sigma^2(I) + (0.03I)^2]$‡.

All the calculations were carried out on a PDP 11/34A computer at the Department of Biophysics, King's College, London, using the SDP crystallographic program system.

Results and Discussion

Our initial ^{195}Pt-{^1H} n.m.r. studies of this Pt^{IV} 2-aminoethanol complex showed a single resonance at δ +284 p.p.m. At 343 K the $^1J(^{195}Pt-^{14}N)$ coupling constant of 195 Hz (equivalent to 273 Hz for ^{15}N) was well resolved. This shift appeared to be surprisingly far removed from that of *cis,cis,trans*-$[Pt(NH_2CH_2CH_2OH)_2Cl_2(OH)_2]$ (+881 p.p.m.) or *cis,cis,trans*-$[Pt(NH_3)_2Cl_2(OH)_2]$ (+860 p.p.m.), although both

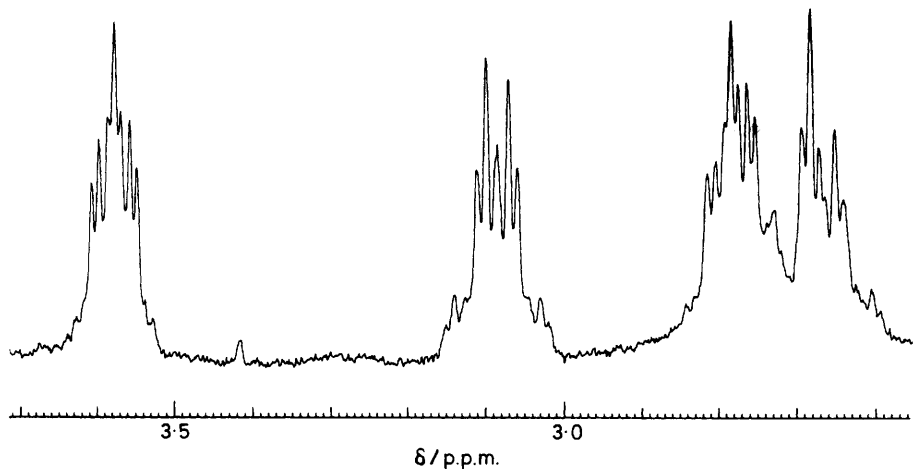

Figure 1. Hydrogen-1 n.m.r. spectrum (400 MHz) of crystals of the title complex dissolved in D_2O showing the four resolved resonances from the NCH_2CH_2O (non-equivalent) protons

Table 1. Fractional atomic co-ordinates with estimated standard deviations in parentheses

Atom	*X/a*	*Y/b*	*Z/c*
Pt	0.059 06(4)	0.223 04(3)	0.261 35(2)
Cl(1)	0.291 2(3)	0.197 4(2)	0.448 0(2)
Cl(2)	0.310 0(3)	0.082 7(3)	0.098 8(2)
O(1)	0.089 5(9)	0.450 9(6)	0.300 4(5)
O(2)	0.019 3(8)	−0.001 8(5)	0.218 6(5)
O(W1)	0.474 6(9)	0.443 0(7)	0.245 0(7)
O(W2)	0.368 8(13)	0.766 1(7)	0.249 9(7)
N(1)	−0.138 7(10)	0.260 5(7)	0.099 4(6)
N(2)	−0.162 3(9)	0.328 9(6)	0.404 1(6)
C(1)	−0.066(2)	0.533 1(10)	0.219 0(8)
C(2)	−0.108(2)	0.400 1(10)	0.074 7(8)
C(3)	−0.165(1)	0.034 7(8)	0.279 0(8)
C(4)	−0.188(1)	0.184 1(8)	0.424 2(7)
H(N11)	−0.27(0)	0.273(0)	0.117(0)
H(N12)	−0.12(0)	0.161(0)	0.008(0)
H(N21)	−0.27(1)	0.377(7)	0.362(6)
H(N22)	−0.13(2)	0.434(11)	0.513(10)
H(C11)	−0.02(2)	0.631(12)	0.207(10)
H(C12)	−0.18(1)	0.577(10)	0.278(9)
H(C21)	−0.23(1)	0.444(9)	0.036(8)
H(C22)	0.00(0)	0.360(0)	0.014(0)
H(C31)	−0.15(0)	−0.061(0)	0.293(0)
H(C32)	−0.28(1)	0.069(8)	0.213(7)
H(C41)	−0.32(0)	0.218(0)	0.461(0)
H(C42)	−0.09(0)	0.155(0)	0.494(0)
H(W11)	0.43(1)	0.551(8)	0.241(7)
H(W21)	0.23(2)	0.822(11)	0.215(10)
H(W22)	0.47(0)	0.824(0)	0.354(0)

have similar $^1J(^{195}Pt-^{14}N)$ coupling (190 and 196 Hz respectively [6]). The ^1H n.m.r. spectrum shows four complex multiplets each equivalent to one proton when measured at high frequency (Figure 1). This suggested that the CH_2-CH_2 region of 2-aminoethanol was held rigidly in the complex, each of these four protons being magnetically non-equivalent. The *X*-ray crystallographic analysis showed that this was the case.

In the crystal, Pt^{IV} has octahedral co-ordination with 2-aminoethanol deprotonated at the OH group and chelated through NH_2 and O^- (Figure 2). There are two water molecules in the lattice, and hence elemental analysis does not distinguish between $[Pt(NH_2CH_2CH_2OH)_2Cl_2(OH)_2]$ and the correct formulation, $[Pt(NH_2CH_2CH_2O)_2Cl_2]\cdot 2H_2O$. Loss

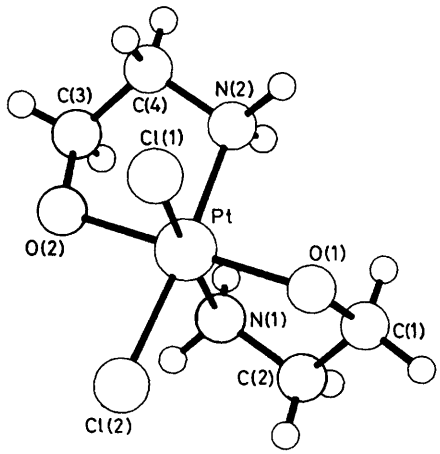

Figure 2. Molecular structure of $[Pt(NH_2CH_2CH_2O)_2Cl_2]$ showing the atom numbering scheme

of water may account for the deterioration of the crystal during data collection. Atomic co-ordinates, and bond lengths and bond angles are listed in Tables 1 and 2 respectively. The two water molecules are involved in weak hydrogen-bonding (Table 3 and Figure 3).

The angle within the chelate ring is much smaller than 90° (Table 2) and the 2-aminoethanolate rings are slightly puckered. The two amino-groups are in the *cis* configuration, one of the major requirements for anti-tumour activity. The sense of twist of the two chelate rings within a molecule of complex is the same (either δ or λ), and the two average chelate rings of a molecule form an angle of 102°.

There are a few reported crystal structures for metal 2-aminoethanol complexes. In bis(2-aminoethanol)bis(isothiocyanato)nickel(II) a bidentate chelate ring is formed without loss of the hydroxyl proton,[7] whereas 2,2′,2″-nitrilotriethanol loses one of its three OH protons to form a tetradentate ligand with Zn^{II} together with intermolecular hydrogen bonds (O–H · · · O).[8] In the binuclear Co^{III}/Ni^{II} complex $[CoNi(NH_2CH_2CH_2OH)_3(NH_2CH_2CH_2O)_3]I_2$, 2-aminoethanol is involved in strong hydrogen bonds.[9] 2-Aminoethanol acts as a unidentate *N*-donor in the complex $[Co^{III}(OCH_2CH_2N{=}CMeCH{=}CMeNCH_2CH_2O)(NH_2CH_2CH_2OH)_2]$. Four of the co-ordination sites are occupied by

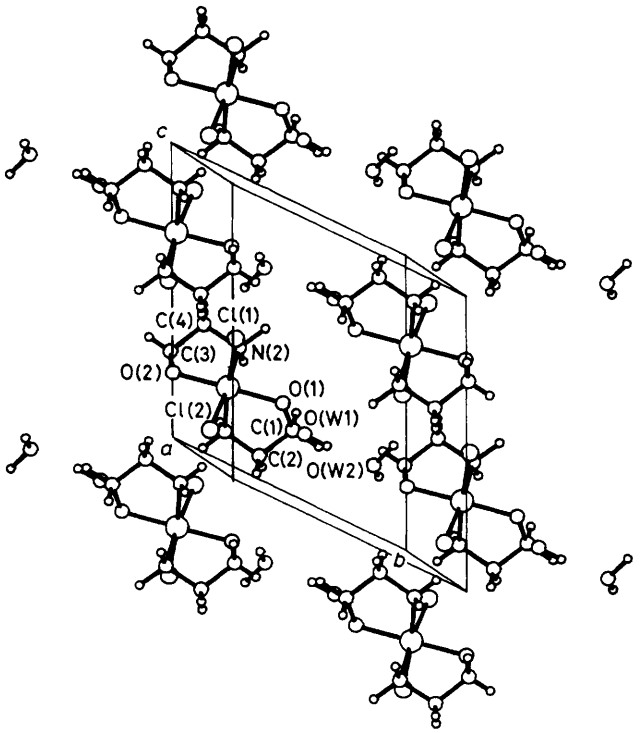

Figure 3. Crystal packing projected on the *bc* plane

Table 2. Bond lengths (Å) and angles (°) with estimated standard deviations in parentheses

Pt–Cl(1)	2.305(2)	N(2)–H(N21)	0.885
Pt–Cl(2)	2.306(2)	N(2)–H(N22)	1.150
Pt–O(1)	2.006(4)	C(1)–H(C11)	1.107
Pt–O(2)	1.998(4)	C(1)–H(C12)	0.954
Pt–N(1)	2.022(5)	C(2)–H(C21)	0.918
Pt–N(2)	2.043(5)	C(2)–H(C22)	0.961
O(1)–C(1)	1.437(9)	C(3)–H(C31)	0.900
O(2)–C(3)	1.429(9)	C(3)–H(C32)	1.007
N(1)–C(2)	1.486(9)	C(4)–H(C41)	0.962
N(2)–C(4)	1.491(8)	C(4)–H(C42)	0.964
C(1)–C(2)	1.503(9)	O(W1)–H(W11)	0.937
C(3)–C(4)	1.505(9)	O(W2)–H(W21)	0.988
N(1)–H(N11)	0.912	O(W2)–H(W22)	1.186
N(1)–H(N12)	0.966		

Cl(1)–Pt–Cl(2)	91.25(6)	O(2)–Pt–N(1)	93.2(2)
Cl(1)–Pt–O(1)	91.0(1)	O(2)–Pt–N(2)	85.5(2)
Cl(1)–Pt–O(2)	91.0(1)	N(1)–Pt–N(2)	93.1(2)
Cl(1)–Pt–N(1)	175.8(1)	Pt–O(1)–C(1)	109.6(4)
Cl(1)–Pt–N(2)	87.9(1)	Pt–N(1)–C(2)	107.7(4)
Cl(2)–Pt–O(1)	90.5(1)	O(1)–C(1)–C(2)	109.9(6)
Cl(2)–Pt–O(2)	90.2(1)	C(1)–C(2)–N(1)	108.3(5)
Cl(2)–Pt–N(1)	88.1(2)	Pt–O(2)–C(3)	107.8(3)
Cl(2)–Pt–N(2)	175.5(1)	Pt–N(2)–C(4)	106.8(4)
O(1)–Pt–O(2)	177.9(2)	O(2)–C(3)–C(4)	111.1(6)
O(1)–Pt–N(1)	84.9(2)	C(3)–C(4)–N(2)	106.8(5)
O(1)–Pt–N(2)	93.9(2)	H(W21)–O(W2)–H(W22)	129.9(5)

the strongly bound tetradentate di-imine ligand leaving two sites *trans* to each other for occupation by 2-aminoethanol.[10]

It seems likely that *trans*-dihydroxy Pt^{IV} complexes owe their anti-tumour activity to *in vivo* reduction to the parent Pt^{II} diaminedichloro-complex, effectively with loss of H_2O_2. The formation of the stable five-membered $Pt{-}NH_2CH_2CH_2O$ chelate ring in the Pt^{IV} 2-aminoethanolate complex probably stabilises Pt^{IV} relative to Pt^{II}, so lowering the reduction potential, hence its low activity in animal anti-tumour screens. The Pt^{II} complex itself, however, displays a similar activity to other related complexes, indicative of *N*-bonded unidentate 2-aminoethanol, although at the moment there are no data to rule out the possibility that ring-opened and ring-closed Pt^{II} complexes exist.

Table 3. Hydrogen-bonded contact distances (Å) and angles (°) *

A–H···B	A–H	H···B	A···B	A–H···B
O(W1)–H(W11)···O(W2)	0.94	1.80	2.73	171
O(W2)–H(W21)···O(2^{I})	0.99	1.77	2.69	155
N(2)–H(N21)···O(W1^{II})	0.89	2.00	2.88	170
N(2)–H(N22)···O(1^{III})	1.15	1.76	2.88	163

Symmetry operations I $x, y+1, z$; II $x-1, y, z$; III $-x, -y+1, -z+1$.

*A = Donor, B = acceptor.

There is much scope for detailed mechanistic studies on the formation and reactions of Pt^{IV} anti-tumour drugs in aqueous media. Recently we have observed[4] the isomerization of *trans,trans,trans*-$[Pt(NH_3)_2Cl_2(OH)_2]$ involving the OH^- and Cl^- ligands when the complex was recrystallized from H_2O but not from aqueous H_2O_2. These studies emphasize that all platinum complexes tested for anti-tumour activity should be fully characterised by as many techniques as possible, preferably including *X*-ray crystallography.

Acknowledgements

We thank the Cancer Research Campaign, the S.E.R.C., and the M.R.C. for support, and Johnson Matthey for a C.A.S.E. Award (to I. M. I.).

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Received 2nd *August* 1982; *Paper* 2/1341